XYY Syndrome in Children With Acute Lymphoblastic Leukemia

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Certain constitutional chromosomal abnormalities increase the risk of malignancy and/or decrease treatment tolerance. We identified two patients with the XYY syndrome among a total of 444 male children with acute lymphoblastic leukemia who had complete cytogenetics studies. In both cases, the leukemic cell karyotype suggested a constitutional XYY abnormality that was confirmed in studies of lymphocytes obtained during remission. The incidence rate in our series is higher than that of the XYY syndrome in the general population (0.0045 vs. 0.001), but not significantly so. This finding and a literature review failed to confirm an increased frequency of the XYY syndrome among children with acute lymphoblastic leukemia. Both of our patients remain in remission 24 and 28 months, respectively, postdiagnosis. Their tolerance of intensive treatment, including high-dose methotrexate, suggests that the untoward treatment toxicity seen in patients with chromosomal abnormalities such as trisomy 21 does not extend to the XYY syndrome. © 1997 Wiley-Liss, Inc.

Key words: XYY, childhood ALL, chromosomal abnormalities

INTRODUCTION

Constitutional chromosomal abnormalities, such as those found in Down, Klinefleter, and Turner syndromes, have been associated with various malignancies [1]. There have also been reports of acute and chronic leukemias in patients with the XYY syndrome [1–13]. The XYY syndrome occurs in approximately 1 per 1,000 live male births and is associated with increased stature and severe acne [14]. It is unknown whether the XYY syndrome is associated with a greater risk of malignancy. Here, we describe two cases of acute lymphoblastic leukemia (ALL) in children with the XYY syndrome. We also review the characteristics and frequency of this combination in the literature and in our experience at St. Jude Children's Research Hospital (SJCRH).

CASE REPORTS

Case 1

A 2-year-old white boy presented to SJCRH with a 2-week history of decreased appetite, pallor, low-grade fever, and malaise. The family history identified a half-sibling with Hodgkin's disease. On physical examination, the patient was pale, but otherwise appeared well. Bilateral cervical adenopathy and hepatosplenomegaly were present. There was no evidence of central nervous system (CNS) leukemia. He had a leukocyte count of 16.6×10^9/L (39% circulating lymphoblasts), a hemoglo bin level of 7.8 g/dL, and a platelet count of 174×10^9/L. A bone marrow examination demonstrated 91% replacement with L2 lymphoblasts (French-American-British [FAB] classification) and an early pre-B phenotype. The leukemic cell DNA index was 1.0. All 18 analyzed metaphases from the marrow sample had abnormal karyotypes. The chromosome morphology of the stem line was fair, and the karyotype 47,XYYc[10] was identified. The other line contained 85–90 chromosomes that could not be analyzed completely, due to poor morphology. The near-tetraploid line appeared to have an XXYYYYc complement, consistent with duplication in the line with 47 chromosomes. Cytogenetic studies performed on phytohemagglutinin (PHA)-stimulated peripheral blood lymphocytes obtained during remission also demonstrated the XYY pattern, establishing the presence of a constitutional abnormality.

The patient was enrolled on our institutional protocol Total XIII, which includes induction (vincristine, daunomycin, L-asparaginase, prednisone, etoposide, and cytarabine), consolidation (high-dose methotrexate, 2 g/m^2 IV, and 6-mercaptopurine, 75 mg/m^2 orally daily), and continuation (vincristine, prednisone, 6-mercaptopurine, standard and high-dose methotrexate, cyclophosphamide, cytarabine, and etoposide) phases. During induction, he experienced no significant sequelae and achieved complete remission. He remains in remission on continuation therapy at 28 months after diagnosis.

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TABLE I. Clinical and Laboratory Features of Patients With ALL and XYY Syndrome*

Feature	Case No. 1	2	3	4	5
Age (years)	2	7	3 1/2	16	15
Mediastinal mass	None	None	NR	None	Yes
Hepatosplenomegaly	Yes	Yes	No	No	NR
CNS involvement	No	No	NR	NR	NR
Hemoglobin (g/dL)	7.8	9.2	NR	NR	NR
White blood cell × (10^9/L)	16.6	7.3	NR	NR	4.4
Platelets × (10^9/L)	174	58	NR	NR	64
FAB morphology	L2	L1	L1	L2	NR
Immunophenotype	Early pre-B	T-cell	NR	Non-T, non-B	NR
DNA index	1.0	1.0	1.18	NR	NR
Karyotype	47,XYYc/85–90, XXYYYYc	47,XYYc[a]	Mosaic XYY/XY	47,XYY	47,XYY
Remission induction	Yes	Yes	Yes	Yes	Yes
Remission duration	28 months +	24 months +	NR	NR	3 months

*Cases 1 and 2 are described in the present paper; case 3 is from reference 13, case 4 from reference 7, and case 5 from reference 6. NR, not reported.
[a]49,XYYc, +X,-2,-5,del(9)(p22),?der(13)t(2;13)(q13;q13),i(17)(q10),+3mar

Case 2

A 7-year-old white boy presented to SJCRH with a 4-week history of fatigue and easy bruising. Physical examination revealed scattered bruises, hepatosplenomegaly, and cervical, axillary, and inguinal adenopathy. His leukocyte count was 7.3 × 10^9/L (1% lymphoblasts), with a hemoglobin level of 9.2 g/dL and a platelet count of 58 × 10^9/L. A sample of cerebrospinal fluid contained no leukemic blast cells. Bone marrow examination showed 26% replacement with FAB L1 lymphoblasts of T-cell lineage; the DNA index was 1.0. All of 20 analyzed metaphases from the bone marrow sample had abnormal karyotypes; the presence of two lines was established. The stem line had the following karyotype: 49, XYYc, +X, −2, −5,del(9)(p22),?der(13)t(2;13)(q13;q13), i(17)(q10),+3mar[19]. The other line had the karyotype 47,XYYc[1]. After successful remission induction therapy, cytogenetic studies of normal bone marrow lymphocytes demonstrated the XYY pattern, confirming a constitutional abnormality.

The patient was enrolled on the Total XIII protocol. He had no untoward side effects during remission induction and achieved a complete remission. At 24 months after diagnosis, he remains in remission and is receiving continuation therapy.

RESULTS AND DISCUSSION

Various malignancies have been reported in patients with the XYY syndrome [1–13,15,16]. Most are hematopoietic malignancies [1–13], including ALL, acute myeloid leukemia, and chronic myelogenous leukemia. One case of medulloblastoma [15] and one of mycosis fungoides [16] have also been reported. Our review of the literature identified seven prior cases of ALL in children with the XYY syndrome. In Table I we summarize features of the three previously reported cases with adequate information as well as our two cases in this retrospective analysis. Age, presence of organomegaly, FAB type, phenotype, and DNA index varied among these five patients. We did not identify any clear morphologic, immunologic, or biologic pattern among these cases.

Whether males with the XYY syndrome have an increased risk of ALL is uncertain. There are no reports of the XYY abnormality among the 330 cases of ALL studied at the Third International Workshop on Chromosomes in Leukemia [17], and there are only two cases of the XYY syndrome among 2,067 newly diagnosed cases of ALL with successful karyotype analysis enrolled in the Pediatric Oncology Group (POG) studies [13]. Taub et al. [13] reported only one case of the XYY defect among 750 newly diagnosed cases of ALL with successful karyotype analysis at the Children's Hospital at Michigan. From 1979 to 1995, we have systematically analyzed leukemic cell chromosomes from all patients newly diagnosed with ALL treated on institutional protocols. During this time period, successful cytogenetic analysis was performed for 444 boys, of whom only the 2 described here had a constitutional XYY pattern. Although this incidence rate appears to be higher than that of the XYY syndrome in the general population (0.0045 vs. 0.001), this difference is not statistically significant (95% confidence interval, 0.00055–0.01618). However, the true incidence of the XYY syndrome in ALL will emerge only when constitutional chromosome analysis is performed for all males with an extra Y chromosome in the karyotype of their leukemic cells. At our institution, 18 of 182 hyperdiploid (51–67 chromosomes) cases had a +Y in the leukemic karyotype (Raimondi, personal communication). Seventeen of these cases had additional diploid metaphases [46,XY]; therefore, the extra Y was considered to be an

acquired numerical abnormality. One case had 54 chromosomes and an extra Y in all the metaphases available for evaluation; a constitutional karyotype has not yet been obtained. Among the 86 hyperdiploid cases with 47–50 chromosomes present, only 1 patient (case number 2) had a +Y in the leukemic karyotype [18].

Both of our patients remain in remission 24 and 28 months after diagnosis, respectively. In contrast, of the previously reported cases (Table I), one patient has relapsed and follow-up information is unavailable for the others. In addition, intensive multiagent remission induction therapy did not cause severe sequelae in either of our patients. Their tolerance of combination chemotherapy including high-dose methotrexate (2 g/m^2) contrasts with the morbidity and severe toxicity in patients with Down syndrome treated on similar regimens [19]. In view of the limited number of cases, however, additional patients must be studied to determine whether children with ALL and the XYY syndrome respond atypically to treatment of their leukemia.

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